REMARKS

Reconsideration of the subject application is requested in view of the above amendments and the following remarks.

I. Amendment to the Specification. The specification has been amended to provide antecedent basis for claimed subject matter. Support for the amendment is found in original claims 1 and 5-9.

II. Claim Status. Claims 1 and 19 have been amended. Claims 5, 6 and 21-35 have been canceled. By this Amendment, claims 1-4 and 7-20 are pending.

Claim 1 has been amended to incorporate the claim limitation previously found in claim 6. Accordingly, support for amended claim 1 is found in original claims 1 and 6. The scope of claim 19 is unchanged. All amendments being supported by the original claims, by this Amendment, no new matter is added to the claims.

Claims 21-35 have been canceled without prejudice or disclaimer following their being withdrawn from consideration by the Examiner as being directed to non-elected subject matter. Applicants specifically reserve the right to pursue all subject matter of the canceled claims in one or more divisional application.

III. Objection to the Specification. The Examiner has objected to the specification as failing to provide proper antecedent basis for the claimed subject. The present amendment to the specification is believed to address the Examiner's objection. Withdrawal of the objection is respectfully requested.

IV. Claim Rejections. The claim rejections set forth in the Office Action are summarized and addressed as follows:

(i) Rejections Under 35 U.S.C. §112, second paragraph. Claim 19 has been rejected as indefinite. The Examiner asserts there is insufficient antecedent basis for the term "variant peptide" in line 1. In response, without conceding the validity of the rejection, claim 19 has been amended. The amendment does not change the scope of claim. Reconsideration of claim 19 and withrawal of the rejection thereof for indefiniteness is requested.

(ii) Rejections Under 35 U.S.C. §112, first paragraph (enablement). Claims 1-19 are rejected as allegedly failing to be enabled by the specification. The Examiner asserts that the specification does not reasonably provide enablement for a peptide epitope sequence that is less than 18 amino acids in length. The rejection is respectfully traversed on the grounds that the Examiner has failed to meet his burden of establishing a *prima facie* case that one of ordinary skill in the art cannot make and use the invention without undue experimentation.

To be enabling, the specification must teach one of ordinary skill in the art to make and use the full scope of the claimed invention without "undue experimentation." *In re Wright,* 999 F.2d 1557, 1561, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993). As long as "undue experimentation" is not involved, a specification complies with the enablement requirement, even if a reasonable amount of routine experimentation is required to practice the invention. *Enzo Biochem Inc. v. Calgene,* 188 F.3d 1362, 1371, 52 U.S.P.Q.2d 1129, 1135 (Fed. Cir. 1999). Even "a considerable amount of experimentation is permissible, if it is merely routine." *In re Wands* 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988).

Furthermore, there is no reason to doubt the objective truth of statements in a patent application specification. *Fiers v. Revel,* 984 F.2d 1164, 1171-1172, 25 U.S.P.Q.2d 1601, 1607 (Fed. Cir. 1993). Because nothing more than objective enablement is required, it is irrelevant whether an enabling teaching is provided through broad terminology or illustrative examples. *In re*

Marzocchi, 439 F.2d 220, 223, 169 U.S.P.Q. 367, 369 (CCPA 1971). The initial burden of establishing a prima facie case of unpatentability based on non-enablement rests on the Examiner. *In re Oetiker,* 977 F.2d 1448, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992). It is the Examiner's burden to provide a reasonable explanation of why the specification does not enable the scope of the pending claims. *In re Wright,* 999 F.2d 1557, 1561-1562, 27 U.S.P.Q.2d 510, 1513 (Fed. Cir. 1993).

The Examiner has failed to provide a "reasonable explanation" of why practicing claims 1-19 requires "undue" experimentation. To support his position that claims 1-19 are not enabled, the Examiner asserts that King et al. teaches that hybrid proteins with 20-30 amino acid residues have maximal reduction in allergenicity while still retaining immunogenicity, that the specification discloses that a hybrid protein with an 8 amino acid peptide epitope sequence resulted in no IgG antibody response, and that Patent Publication US 2004/0171116 A1 (the " '116 Publication") teaches that insertion of a peptide fragment of from an insect allergen into an insect scaffold will in many cases lead to destablized molecules unsuitable for use in vaccination and that since epitopes are almost never linear this approach is not suitable for "grafting" three dimensional epitopes from allergens to scaffold proteins. Each of the Examiner's arguments are examined in turn.

First, whether or not hybrid proteins with 20-30 amino acid residues have "maximal reduction" in allergenicity while still retaining immunogenicity is of no consequence with regard to enablement. Enablement requires only that the specification teach one of ordinary skill in the art how to practice the claimed invention without undue experimentation. There is no requirement that Applicants claim only the "maximal" embodiment of the invention. Theclaims are drawn to "[a]n allergen hybrid protein having reduced allergenicity but retaining immunogenicity." Whether some

hybrid allergens have more highly reduced allergenicity and/or retain more immunogenicity is of no consequence.

Second, the Examiner's assertion that the specification discloses that a hybrid protein with an 8 amino acid peptide epitope sequence resulted in no IgG antibody response does not support the Examiner's position that the specification does not provide enablement for a peptide sequence that is less than 18 amino acids in length. Nothing more than objective enablement is required. *In re Marzocchi,* 439 F.2d at 223, 169 U.S.P.Q. at 369. The enablement requirement may be satisfied even though a claim encompasses inoperable embodiments. It is not necessary that all claimed embodiments are operable or that the applicant has tested all of them. *Atlas Powder Co. v. E.I. duPont de Nemours & Co.,* 750 F.2d, 1569, 1576, 224 U.S.P.Q.2d, 409, 414 (Fed. Cir. 1984).

Moreover, the specification discloses that hybrid EA-PV195-204, bearing only a ten amino acid epitope of Ves v 5, produced 0.4 mg of Ves v 5 specific IgG/ml of serum. See specification at page 55, Table 3A, set A. The Examiner's assertion that Applicants' working examples are limited to peptides of greater than 18 amino acids is thus not correct. In light of Applicants' actual reduction to practice of the invention using an a 10 amino acid epitope and the lack of any credible evidence to the contrary, there is reason to doubt the specification's disclosure that the invention can be practiced with epitopes of 6 amino acids.

Lastly the '116 Publication's statements that that insertion of peptide fragments from an insect allergen into an insect scaffold leads "in many cases" leads to destabilization and that because epitopes "almost never consist of a linear peptide fragment, this approach is not suitable for grafting" are mere conclusions that are refuted by the instant specification. Hence, the specification discloses at page 50, lines 9-19:

> Recombinant Ag 5s and hybrids showed nearly identical CD spectra as those of the natural Ag 5s (Fig. 7). The spectra of the natural Ves v 5 and the EA-Ves v 5, and those of EA-PV1-46, EA-PV1-155 and EA-PV156-204 showed the presence of minima at about 208 nm with a shoulder at 225 nm (Fig. 7). These features are indicative of an ordered feature (Yang et al., 1986, Methods in Enzymology 130:208). Similar CD spectra were observed for the other hybrids listed in Table II (data are not shown). The CD spectrum of recombinant Ves v 5 from bacteria showed a minima at about 200 nm, which is indicative of a disordered structure (Monsalve et al., 1999, Protein Expr. Purif. 16:410).
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> The recombinant Ag 5s and hybrids from yeast were freely soluble in acid or basic buffers, as were the natural Ag 5s. This is in contrast to recombinant vespid Ag 5s from bacteria, which were freely soluble only in acidic buffer.

Table 2 on pages 51-52 of the specification includes hybrid proteins representing 11 different fusions of Ves v 5 and Pol a 5 sequences, including several hybrids with epitopes that are 9-11 amino acids long (EA-PV142-150, EA-PV195-204, EA-PV22-32 and EA-PV115-125). Hence, the instant specification enables one of ordinary skill in the art to make hybrids bearing short linear peptide epitopes that are immunogenic without undue experimentation.

For all of the reasons set forth above, the rejection of claims 1-19 under 35 U.S.C. §112, first paragraph, for lack of enablement should be withdrawn. Reconsideration of claim 1-19 is requested.

(iii) Rejections Under 35 U.S.C. §102. Claims 1-6 and 10-17 have been rejected as allegedly anticipated by Monsalve et al., *Allergy Clin. Immunol.* 103(1) Part 2:S181, 1999 ("Monsalve I") or Monsalve et al., *Arb. Paul Ehrlich Inst.* 93:181-188, 1999 ("Monsalve II"), as evidenced by King et al., *Intl. Arch. Allergy Immunol.* 124:85-86, 2001 ("King et al."). In response, without conceding the validity of the rejection, claim 1 has been amended to be directed to peptide epitopes that are about 6 to about 45 amino acids in length. The Examiner concedes that the prior

art fails to disclose the claimed hybrid allergens comprising a peptide epitope that is about 6 to about 45 amino acids in length. The present rejection should therefore be withdrawn.

Moreover, the Examiner's assertion that 49 amino acids "reasonably reads" upon 45 amino acids is in error. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California,* 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the patent claim." *Richardson v. Suzuki Motor Co.,* 868 F.2d 1226, 1236, 9 U.S.P.Q.2d 1913, 1920 (Fed. Cir. 1989). None of the prior art cited by the Examiner discloses the claimed invention in "complete detail." The prior art cited by the Examiner therefore does not anticipate the claimed invention.

(iv) Rejections Under 35 U.S.C. §103. Claims 1 and 18 are rejected as allegedly obvious over either Monsalve I or Monsalve II, as evidenced by King et al., in view of Alibhai et al., U.S. Patent No. 6,639,054 ("Alibhai et al."). In response, without conceding the validity of the rejection, claim 1 has been amended.

None of the prior art cited by the Examiner, alone or in combination, suggests the claimed hybrid allergens comprising an peptide epitope in a scaffold protein, wherein the peptide epitope is about 6 to about 45 amino acids in length. The hybrid proteins of Monsalve I and and Monsalve II include peptide epitopes that are 49 amino acids in length. There is no suggestion or incentive in Monsalve I or II to make hybrid allergens bearing smaller peptide epitopes. Nor does Alibhain et al. suggest or afford any incentive to shorten the epitopes used in the hybrid proteins of Monsalve I and II. For at least this reason, amended claim 1 is not obvious over the prior art of record. Each of remaining claims 2-4 and 7-20 depend either directly or indirectly from claim 1. Claims 2-4 and 7-20 therefore are also not obvious over the prior art of record.

Additionally, Applicants traverse the Examiner's attempt to use Alibhai et al. to modify the hybrid allergens disclosed in Monsalve I and II to include a conservative mutation. Alibhai et al. is concerned with insecticidal protein, which upon application will be expressed in the target plant and which may subsequently be eaten and thereby elicit an allergic reaction in an individual suffereing from allergy to the particular allergen, i.e., to the insecticidal protein. Alibhai et al. teach modification of the insecticidal protein to obtain hypoallergenic variants with retained insecticidal activity.

Alibhai et al. stands mererly for the proposition that mutating an allergen may reduce IgE binding. Alibhai et al., however, provides no motivation to make a conservative amino acid change in an epitope of a hybrid allergen protein wherein the epitope retains the immunogenecity of the native allergen. Because Alibhai et al. is concerned solely with retaining insecticial acivity of the modified protein, there is no motivatin or suggestion of success in Alibhain et al. to make mutations in a peptide eptiope as opposed to the scaffolding portion of a hybrid allergen while, at the same time, retaining immunogenicity of the native allergen, as required in the instant claims. For at least this reason, additionally, the intant claims are not obvious over Monsalve I or II over Alibhai et al.

For the reasons set forth above, the instant claims are not obvious over the Monsalve I or II in view of Alibhai et al. Reconsideration of the claims and withdrawal of the instant rejection thereof as obvious over the prior art of record is requested, accordingly.

CONCLUSION

In view of the above remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Dated: July 1, 2005

Respectfully submitted,

By _____

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